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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,693	ARATHOON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050609*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. The amendment filed June 9, 2005 is acknowledged and has been entered. Claims 52-87 have been canceled. Claims 88-109 have been added.

2. Claims 88-109 are pending in this application and are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following Office action contains NEW GROUNDS of objection and rejection necessitated by amendment.

Information Disclosure Statement

5. The information disclosure filed June 9, 2005 has been considered. An initialed copy is enclosed.

Grounds of Objection and Rejection Withdrawn

6. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 16, 2005.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

7. The rejection of claims 88-109 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description rejection"; this ground of rejection is set forth in section 10 of the preceding Office action mailed March 16, 2005.

At pages 10-12 of the amendment filed June 9, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the specification and, in particular, Tables 4 and 5, Figures 4 and 8, and pages 99 and 100 provide an adequate written description of the claimed invention to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph. Applicant has remarked that Figure 4, for example, shows the sequence of several light chain variable domains from antibodies specific for different antigens that have amino acid sequences that are at least 98% identical and only differ from the others at positions outside the complementarity-determining regions (CDRs). It is possible to envision a bispecific antibody that comprises a light chain variable domain that commonly functions in conjunction with two different heavy chain variable domains to bind the different antigens to which antibodies comprising the different heavy chain variable domains and this common light chain bind; this is because, if two different antibodies that bind different antigens comprise identical light chains, the light chains of these different antibodies must necessarily be capable of substituting for one another and function in conjunction with the different heavy chains of which the different antibodies are also comprised to bind the different antigens (i.e., the light chains of the different antibodies are structurally identical and therefore functionally equivalent). However, as explained in the preceding Office action, it is not possible to immediately envision, recognize or distinguish bispecific antibodies comprised of a light chain variable domain that commonly functions in conjunction with two different heavy chain variable domains to bind the different antigens to which antibodies comprising the different heavy chain variable domains bind, where such antibodies do not also comprise a common (i.e., structurally identical) light chain variable domain.

Figure 6, for example, lists 4 antibodies that bind Ob-R (i.e., O7, O8, O9, and 012), which comprise light chains that are identical to the light chain of antibody that binds HER3 (i.e., H2); however, the figure also lists 14 other antibodies that bind Ob-R, which comprise light chains that have amino acid sequences that vary substantially from the amino acid sequence of the light chain of this antibody that binds HER3. For example, the anti-Ob-R antibody O1 has only 47% identity to the amino acid sequence of the light chain of the anti-HER3 antibody H2. The anti-Ob-R antibody O16 has only 80% identity to the amino acid sequence of the light chain of the anti-HER3 antibody H2, but even so, because of the differences in their amino acid sequences, it would not be immediately appreciated that the light chain of anti-Ob-R antibody is functionally equivalent to the light chain of the anti-HER3 antibody. In fact, as the record shows, the skilled artisan cannot reliably predict the functional consequence of amino acid sequence variations and therefore, unless the light chains of two antibodies binding two different antigens are known to be structurally identical, it cannot be reliably predicted which antibodies that bind any two different antigens comprise light chains that are functionally equivalent and capable of substituting for the other in a bispecific antibody that retains the ability to bind both these different antigens. Only in the instances disclosed, where the light chains of the antibodies binding the different antigens are identical, would it be immediately appreciated that the light chain of one of the antibodies could substitute for the other; and only in such instances could the light chain of either antibody be used to construct a bispecific antibody comprising the different heavy chains of which the different parental antibodies are comprised, which retains the ability to bind to both of the antigens to which the parental antibodies bind.

In order to further clarify these issues, it is noted that the claims do not require that the light and heavy chain variable domains that form either one of the antigen-binding sites of the bispecific antibody be derived from the same antibody. While the claims recite that the light chain variable domains that interact with the different heavy chain variable domains to form antigen-binding domains that bind different antigens are similar, differing only outside the CDRs, or are identical, the light chain variable domains of the bispecific antibodies are not necessarily derived from either of the different

antibodies from which the heavy chain variable domains is derived. If the bispecific antibody is comprised of a heavy chain derived from one antibody that binds a particular antigen and a light chain derived from another antibody that also binds this particular antibody, even thought the light chain may be structurally identical to the light chain of a third antibody that binds another antigen, it cannot be predicted whether the light chain of the bispecific antibody will form an antigen-binding site capable of binding the particular antigen, since the light chain is only known to form such an antigen-binding site with the heavy chain of the other antibody; in other words, it cannot predicted whether the light chains of one or another antibody that binds a particular antigen are functionally equivalent, unless it is first known that the light chains of these different antibodies are structurally identical. Accordingly, it does not suffice to adequately describe a genus of bispecific antibodies comprising two different antigen-binding sites comprised of different heavy chain variable domains and an identical or similar light chain variable domain by merely describing a few examples of antibodies that bind a few different antigens, which comprise light chains that are more or less similar or otherwise identical. The two different arms of the bispecific antibodies to which the claims are directed do not necessarily retain the binding specificities of the antibodies comprising light chain polypeptides that are similar or identical to the bispecific antibodies' light chain polypeptides; so, unless the bispecific antibody is comprised of light chain variable domains that are known to interact with heavy chain variable domains to form an antigen-binding site that is capable of binding a particular antigen, the artisan could not immediately envision, recognize or distinguish members of the genus of bispecific antibodies to which the claims are directed.

The claims are directed to bispecific antibodies comprising light chain polypeptides that are capable of interacting with different heavy chain polypeptides to form different antigen binding domains; the light chain polypeptides of which these different antigen binding domains are comprised are either identical or at structurally similar, differing only at positions outside the CDRs. Nonetheless, the written description requirement is still not met. By definition, the bispecific antibody binds two different antigens. Because the light chain polypeptides of which the bispecific antibody

is comprised interact with a first and a second antibody heavy chain polypeptide to form an antigen-binding domain that binds a first and a second antigen, respectively, despite structural similarity or identity, the light chain polypeptides necessarily function differently as part of the bispecific antibody, since specificities of the different arms of the antibody differ. Consequently, there is no correlation between any one particularly identifying and substantial structural feature and any one particularly identifying functional feature (e.g., binding specificity), which would enable the artisan to immediately envision, recognize, or distinguish members of the genus of bispecific antibodies to which the claims are directed. Moreover, because the two different arms of the bispecific antibodies do not necessarily retain the binding specificities of the antibodies comprising light chain polypeptides that are similar or identical to the bispecific antibodies' light chain polypeptides, the bispecific antibodies possess *any* binding specificity, not necessarily the binding specificities of the "parent antibodies". Accordingly, as explained above, there is no correlation between the presence of "a common sequence", or an amino acid sequence that is at least 98% identical to the amino acid sequence of other light chain polypeptides and any one particularly identifying functional feature (e.g., binding specificity).

Applicant has remarked that at page 98, line 5, through page 101, line 19, the specification shows an actual reduction to practice of an method for producing a bispecific antibody having binding specificity for Ob-R and HER3. The example to which Applicant has referred is not representative of the genus of bispecific antibodies produced by the claimed methods and host cells, since the bispecific antibodies to which the claims are directed may bind any antigen and may be comprised of light and heavy chain variable domains of any antibody. Therefore, considering the vastly disparate structures and functions of the bispecific antibodies produced by the claimed methods and host cells, and the fact that one cannot predict the structures of light chain variable domains that will commonly function in conjunction with different heavy chain variable domains to bind any two different antigens, the single example of a bispecific antibody that binds Ob-R and HER3 would not reasonably convey Applicant's possession of the claimed invention at the time the application was filed.

Applicant has disagreed with the contention that the claims do not require that the bispecific antibody produced by the claimed methods or by the claimed host cells retains the binding specificities of each of the parent antibodies. Applicant's remark is noted; however, the claims do not require that that the bispecific antibody produced by the claimed methods or by the claimed host cells retain the binding specificity of each of the parent antibodies. Accordingly, as explained in the preceding Office action, the claims are directed to methods for producing bispecific antibodies comprising components of "parental" antibodies that bind different antigens, but which do not necessarily have the same binding specificities as the parental antibodies from which they are derived. Therefore, given that the function of the bispecific antibodies produced by the claimed methods and host cells may vary (i.e., the bispecific antibodies may bind any antigen, not necessarily the same antigens to which the parental antibodies bind), there is no correlation between a particularly identifying structural feature shared by the bispecific antibodies and a particularly identifying functional feature also common among the bispecific antibodies, such that that skilled artisan could immediately envisions, recognize or distinguish at least a substantial number of the members of the genus of bispecific antibodies produced by the claimed methods and host cells.

It is again noted that the supporting disclosure *would be sufficient* to adequately describe a method for preparing a bispecific antibody comprising a first and a second light chain polypeptide that is at least 98% identical to the light chain polypeptides of a first and a second antibody that binds a first and a different second antigen, wherein said first and second light chain only differ from the other at positions outside the CDRs and wherein said bispecific antibody retains the ability to bind both the first and second antigen, since, in such instances, *a correlation necessarily exists* between a recited structural feature that is common to both light chain polypeptides of the genus of light chain polypeptides of which the bispecific antibodies are comprised and specific functional features attributable to the presence of those common structural features. Therefore, it again suggested that Applicant remedy this issue by amending the claims to recite that the bispecific antibody retains the binding specificity of two antibodies that

bind different antigens, which each comprise a light chain having a variable domain that is at least 98% identical to the light chain of the other antibody and differs from the other only at positions outside the CDRs. As previously suggested, the claims should also be amended to recite additional process steps including the functional antigen-specific screening of a phage display library comprised of antibodies comprising a plurality of heavy chain polypeptides and one or more variable light chain polypeptides having amino acid sequences that are at least 98% identical, the isolation of identified phage comprising nucleic acid encoding antigen-specific antibodies, and the cloning of the encoding nucleic acid into an expression vector for expression in a host cell, and introducing the expression vector into the host cell.

8. The rejection of claims 88-91, 94-99, and 102-107 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for preparing a bispecific antibody comprising a first and a second heavy chain polypeptide and a light chain polypeptide that is capable of interacting with said first and second heavy chain polypeptides to form different antigen-binding sites that bind a first and a different second antigen, wherein said bispecific antibody binds both said first and different second antigen, said method comprising antigen-specific screening of a phage display library comprised of "parent" antibodies comprising a plurality of heavy chain polypeptides and a variable light chain polypeptide, identifying two "parent" antibodies having binding specificity for a first and a different second antigen, isolating the identified phages comprising a nucleic acid encoding said antigen-specific "parent" antibodies, cloning the encoding nucleic acids from the isolated phages into an expression vector to express in a host cell of a bispecific antibody comprising a first arm having the binding specificity of the first "parent" antibody for said first antigen and a second arm having the binding specificity of the second "parent" antibody for said different second antigen, introducing the expression vector into the host cell, culturing the host cell such that the nucleic acid encoding the bispecific antibody is expressed, and recovering the bispecific antibody from the host cell culture, **does not reasonably provide enablement for using** a method for preparing a bispecific antibody comprising

a variable light chain polypeptide selected to have a common sequence or having at least 98% identity to the other variable light chain polypeptide of the bispecific antibody, which may, but not necessarily differ from the other only at positions outside the CDRs, said method comprising culturing a host cell comprising a nucleic acid encoding the variable light chain polypeptide and a first and second "variable heavy chain polypeptide" such that the nucleic acid is expressed and recovering the bispecific antibody, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection of claims 92, 93, 100, 101, 108, and 109 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** a host cell comprising a nucleic acid encoding a bispecific antibody comprising a first and a second heavy chain polypeptide and a light chain polypeptide that is capable of interacting with said first and second heavy chain polypeptides to form different antigen-binding sites that bind a first and a different second antigen, wherein said bispecific antibody binds both said first and different second antigen, **does not reasonably provide enablement for making** a host cell comprising a nucleic acid encoding a bispecific antibody comprising a variable light chain polypeptide selected to have a common sequence or having at least 98% identity to the other variable light chain polypeptide of the bispecific antibody, which may, but not necessarily differ from the other only at positions outside the CDRs, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This is a "scope of enablement rejection"; this ground of rejection is set forth in section 11 of the preceding Office action mailed March 16, 2005.

At pages 12-15 of the amendment filed June 9, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the skilled artisan to make and use the claimed invention without undue experimentation, since the bispecific antibodies will not need to be screened against a magnitude of antigens. Furthermore, given the examples provided in the specification, Applicant has argued that it is routine to determine the amino acid sequence of the light chains of antibodies, such that it is possible to identify two antibodies having the ability to bind different antigens that have light chains that are similar, differing only outside the CDRs, or which are otherwise identical. In addition, Applicant has submitted that the skilled artisan could utilize publicly available databases of the amino acid sequences of antibodies to identify antibodies that bind different antigens, which comprise light chains that are similar, differing only outside the CDRs, or otherwise identical. In response, the examples provided in the specification are not reasonably commensurate in scope with the breadth of the claims. The claims are not limited to a method for preparing a bispecific antibody comprising a first and a second heavy chain polypeptide and a light chain polypeptide that is capable of interacting with said first and second heavy chain polypeptides to form different antigen-binding sites that bind a first and a different second antigen, wherein said bispecific antibody binds both said first and different second antigen, said method comprising antigen-specific screening of a phage display library comprised of "parent" antibodies comprising a plurality of heavy chain polypeptides and a variable light chain polypeptide, identifying two "parent" antibodies having binding specificity for a first and a different second antigen, isolating the identified phages comprising a nucleic acid encoding said antigen-specific "parent" antibodies, cloning the encoding nucleic acids from the isolated phages into an expression vector to express in a host cell of a bispecific antibody comprising a first arm having the binding specificity of the first "parent" antibody for said first antigen and a second arm having the binding specificity of the second "parent" antibody for said different second antigen, introducing the expression vector into the host cell, culturing the host cell such that the nucleic acid encoding the bispecific antibody is expressed, and recovering the bispecific antibody from the host cell culture; nor are the claims limited to a host cell comprising a nucleic acid encoding a bispecific antibody comprising a first and a second heavy chain polypeptide and a light chain polypeptide that is

capable of interacting with said first and second heavy chain polypeptides to form different antigen-binding sites that bind a first and a different second antigen, wherein said bispecific antibody binds both said first and different second antigen. Furthermore, the claims do not require the bispecific antibodies to retain the binding specificity of the parental antibodies from which their components are derived; and moreover, the claims do not require that the light and heavy chain variable domains that form one or the other antigen-binding site are comprised of light and heavy chain variable domains derived from the same antibodies that bind one or the other antigen. One cannot predict the structures of light chain variable domains that will commonly function in conjunction with different heavy chain variable domains to bind any two different antigens. Only in the instances disclosed, where the light chains of the antibodies binding the different antigens are identical, would the light chain of one of the antibodies be expected to substitute for the other; and only in such instances could the light chain of either antibody be used to construct a bispecific antibody comprising the different heavy chains of which the different parental antibodies are comprised, which retains the ability to bind to both of the antigens to which the parental antibodies bind, without undue experimentation. In addition, if the bispecific antibody is comprised of a heavy chain derived from one antibody that binds a particular antigen and a light chain derived from another antibody that also binds this particular antibody, even thought the light chain may be structurally identical to the light chain of a third antibody that binds another antigen, it cannot be predicted whether the light chain of the bispecific antibody will form an antigen-binding site capable of binding the particular antigen, since the light chain is only known to form such an antigen-binding site with the heavy chain of the other antibody. In other words, it cannot predicted whether the light chains of one or another antibody that binds a particular antigen are functionally equivalent, unless it is first known that the light chains of these different antibodies are structurally identical; therefore, unless the claims require that the light and heavy chain variable domains that form one or the other antigen-binding site to be comprised of light and heavy chain variable domains derived from the same antibodies that bind one or the other antigen, the claimed invention could not be made and used without undue experimentation.

Applicant has disagreed with the contention that the functional consequences of amino acid sequence variations in the primary structures of antibodies cannot be predicted; however, Applicant has provided no factual evidence to suggest that contrary to this contention, such consequences are predictable or that despite such unpredictability, it would not require undue experimentation to make and use the claimed invention.

Furthermore, Applicant has suggested that the references cited to support the contention are old and no longer reflective of the state of the art in light of recent advances in technology. In reply, Applicant is reminded that the filing date sought by Applicant in this instance is May 2, 1997; as Applicant has noted, the references purported to be over 15 years old were published in 1987 and 1989. Accordingly, the references cited are submitted to establish the state of the art at the time the application was filed.

Applicant has noted that Caldas et al. teaches a change in the framework of an antibody lowered the binding affinity of the antibody without altogether obviating the antibody's ability to bind the antigen. Nevertheless, the art is unpredictable, as the consequence of the variation in amino acid sequence was not predicted and the change could have instead precluded binding to the antigen, or it could have increased its affinity for the antigen. Therefore, it is submitted that the fact that Caldas et al. teaches a single example of a change in the amino acid sequence of the framework of an antibody that lowers the affinity of the antibody without eliminating its function does not fairly suggest that contrary to the position of the Office, undue experimentation would not be required to make and use the claimed invention.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Double Patenting

9. The provisional rejection of claims 88-109 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-43 and 45-55 of copending Application No. 09/373,403 is maintained. Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons set forth in section 16 of the preceding Office action mailed March 16, 2005.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's amendment filed June 6, 2005 has not addressed this ground of rejection.

10. The provisional rejection of claims 88-109 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 8-16 of copending Application No. 10/143,437 is maintained. Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons set forth in section 17 of the preceding Office action mailed March 16, 2005.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's amendment filed June 6, 2005 has not addressed this ground of rejection.

11. Applicant is again reminded that claims 88-109 are directed to an invention not patentably distinct from claims 1-3 and 8-16 of commonly assigned copending Application No. 10/143,437. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in section 10.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/143,437, discussed above,

would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Applicant's amendment filed June 6, 2005 has not addressed this issue.

New Grounds of Rejection

12. Claims 88-109 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 88-101 are indefinite because claims 88, 92, 94, and 100 recite, "a first antibody variable heavy chain domain specific for a first antigen", "a second antibody variable heavy chain domain specific for a second antigen", and "a variable light chain specific for the first antigen and a variable second chain specific for the second antigen". Claims 102-109 are indefinite because claims 102 and 108 recite, "a first antibody variable heavy chain domain specific for a first antigen", "a second antibody variable heavy chain domain specific for a second antigen", "a first variable light chain specific for the first antigen", and "a variable second chain specific for the second antigen". An antibody binds specifically to an antigen; accordingly, an antibody is said to be specific for an antigen. However, neither a variable domain of light nor heavy chain alone is said to be specific for an antigen, as neither domain alone binds specifically to an antigen. Moreover, in this instance, the variable domain of the light

chain necessarily functions in conjunction with the variable domains of the different heavy chains of the bispecific antibody to bind different antigens; therefore, for this reason also, the light chain cannot be described as having binding specificity for a first or second antigen. For these reasons, the metes and bounds of the subject matter that Applicant regards as the invention are not adequately delineated by the claims, so as to enable the artisan to recognize or determine infringing subject matter, and consequently the claims fail to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

This issue may be remedied by amending, for example, claim 88 to recite "a first antibody variable heavy chain domain of an antibody specific for a first antigen", "a second antibody variable heavy chain domain of an antibody specific for a second antigen", and "a variable light chain of an antibody specific for the first antigen and a variable second chain of another antibody specific for the second antigen".

13. Claims 102-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter' rejection.

Claims 102 and 109 recite, "a variable light chain polypeptide, wherein the variable light chain polypeptide [...] has at least 98% amino acid sequence identity [...] to both of the first and second variable light chain domains", wherein the first and second variable light chain domains are a first variable light chain domain specific for a first antigen and a second variable light chain domain specific for a second antigen. The specification, including the claims, as originally filed, appears to provide written support for a bispecific antibody comprising a variable light chain polypeptide having at least 98% amino acid sequence identity to *either* a first or a second variable light chain domain of two different antibodies that bind a first or second antigen, respectively; however, it does not appear to provide written support for a bispecific antibody

comprising a variable light chain polypeptide having at least 98% amino acid sequence identity to *both* a first and a second variable light chain domain of two different antibodies that bind a first or second antigen, respectively.

This issue might be remedied if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, that are believed to provide proper written support for the claim language.

Conclusion

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
August 15, 2005

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER